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Introduction

Frontotemporal dementia (FTD) accounts for 5–15% of all cases of dementia, and is the second most common cause of dementia in the presenile age group (<65 years of age).[1,2] FTD is a clinical syndrome that is characterized by progressive deterioration in behaviour, personality and/or language, with relative preservation of memory.[3–5] Clinical subtypes of FTD include the behavioural variant (bvFTD) and two forms of primary progressive aphasia: progressive nonfluent aphasia (PNFA) and semantic dementia. Additionally, FTD is often associated with an extrapyramidal movement disorder (parkinsonism or corticobasal syndrome) and/or motor neuron disease.[6,7] Given this variability in phenotype, it is not surprising that the molecular basis of FTD is also heterogeneous (Table 1).

A family history of FTD, often showing an autosomal dominant pattern of inheritance, is present in 25–50% of cases, indicating a strong genetic component.[8,9] In 1998, mutations in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 were identified in a number of families with FTD and parkinsonism.[10–12] Since then, 44 different *MAPT* mutations have been reported, accounting for 5–20% of cases of familial FTD.[13,14] However, a number of chromosome 17-linked FTD families remained in whom no *MAPT* mutations were found.

A major breakthrough occurred in 2006 when the progranulin (*GRN*) gene was identified as the second FTD-related gene on chromosome 17.[15,16] Indeed, *GRN* mutations account for an even larger proportion of FTD families than do mutations in *MAPT*.[13] Much less common are mutations in the valosin-containing protein (*VCP*) gene, which cause the rare familial syndrome of inclusion body myopathy with Paget disease of bone and FTD,[17] and a mutation in the gene encoding charged multivesicular body protein 2B (*CHMP2B*), which was found in a large Danish FTD pedigree.[18] In addition, several families with a combination of FTD and amyotrophic lateral sclerosis (ALS) have been reported to have genetic linkage to a locus on chromosome 9p.[19–27] Despite years of intense effort by many research groups worldwide, the identity of the FTD–ALS gene on chromosome 9p remained elusive until 2011, when two independent studies identified the defect as being an expanded hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 (*C9orf72*) gene.[28,29] Discovery of the *C9orf72* mutation has generated tremendous excitement in the FTD and ALS research communities, as it seems to be the most common genetic cause of both conditions.

The neuropathology associated with clinical FTD is also heterogeneous.[30] A common feature of this disease is the relatively selective degeneration of the frontal and temporal lobes, and the term 'frontotemporal lobar degeneration' (FTLD) is often used for pathological conditions that predominantly or commonly present with FTD. In addition, most cases of FTLD are found to have abnormal intracellular accumulation of a disease-specific protein; as a result, classification of FTLD into broad categories on the basis of the molecular defect thought to be

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R. Rademakers declares an association with the following organization: Mayo Clinic. See the article online for full details of the relationship. The other authors declare no competing interests.

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Key points

- All common frontotemporal dementia (FTD)-causing genes and signature proteins have now been discovered
- Regulation of progranulin—one of the proteins affected in FTD—is one potential therapeutic strategy for this disorder
- Expansion of a GGGGCC hexanucleotide repeat in a noncoding region of the *C9orf72* gene is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS)
- The pathomechanism of *C9orf72* mutation may include haploinsufficiency and/or toxic RNA foci
- Most tau/TDP-negative frontotemporal lobar degeneration (FTLD) cases are characterized by inclusions that are immunoreactive for fused in sarcoma (FUS) and the other FET proteins (EWS and TAF15)
- Differential involvement of the FET proteins in ALS with *FUS* mutations compared with FTLD-FUS implies that different pathomechanisms are involved in each disease

most characteristic of the disease has become a popular approach.[31,32] Initially, only the FTLD subgroup characterized by the aggregation of hyperphosphorylated tau protein in neurons and glia, classified as FTLD-tau, was well-understood (Table 1). However, most cases of FTD are not associated with tau pathology, but are instead characterized by neuronal inclusions that were originally identified using immunohistochemistry for ubiquitin —these cases were consequently termed FTLD-U.[33,34]

Just months after publication of the studies in which the *GRN* mutations were discovered, another landmark paper reported TAR DNA-binding protein 43 (TDP-43) as the ubiquitinated pathological protein in most cases of FTLD-U (subsequently renamed FTLD-TDP), as well as in the majority of ALS cases.[35,36] This finding provided strong evidence that FTD and ALS are closely related conditions with overlapping molecular pathogenesis. This concept was further strengthened in 2009 when, following the discovery that mutations of the fused in sarcoma (*FUS*) gene cause autosomal dominant ALS,[37,38] it was shown that the majority of the ~10% of FTLD patients who do not have either tau or TDP-43 pathology can be characterized by inclusions that are immunoreactive for FUS (a condition termed FTLD-FUS).[39–41] More recently, the FUS-positive inclusions in FTLD-FUS were found to also stain positively for other members of the FET family of DNA/RNA-binding proteins, including Ewing sarcoma protein (EWS) and TATA-binding protein-associated factor 15 (TAF15).[42]

Over the past few years, the pace at which our knowledge of the molecular genetics and neuropathology of FTD has advanced has been truly remarkable (Box 1). In just over 5 years, we have gone from knowing virtually nothing of the molecular basis of most cases of FTD, to now being able to determine the genetic cause in the majority of autosomal dominant families, and being able to assign virtually all cases of FTLD to one of three major pathological subtypes: FTLD-tau, FTLD-TDP or FTLD-FUS.[32] This insight is a crucial step towards improved care for patients with FTD, as it provides the basis for more-informed counselling and the potential for more-specific diagnostic tests and targeted therapies. In this Review, we highlight several recent advances in our understanding of the molecular aspects of FTD, focusing on the discovery of the *C9orf72* mutation and the roles of progranulin, TDP-43, and FUS and the other FET proteins in disease pathogenesis.

Table 1 | Genetic and clinical correlates of the molecular subtypes of FTD

Molecular classification	Pathological subtype*	Associated genes‡	Associated clinical phenotypes				
			bvFTD	PNFA	SD	Parkinsonism	MND
FTLD-tau		*MAPT*	+	(+)	(+)	+	ALS, PLS
	PiD		+	+	(+)	+	PLS
	CBD		+	+		+	PLS
	PSP		+	+		+	PLS
	AGD		+			+	PLS
	NFT-dementia		+				
	MSTD		+				
	WMT-GGI		+				
FTLD-TDP		(*TARDBP*)	(+)			+	ALS
	Type A	*GRN*	+	+	(+)	+	ALS
	Type B	*C9orf72*	+	+	+	+	ALS
	Type C	*VCP*	+			(+)	
	Type D		+				
FTLD-FUS		(*FUS*)	(+)				ALS
	aFTLD-U		+			+	PLS
	NIFID		+			+	ALS
	BIBD		+				
FTLD-UPS							
	FTD-3	*CHMP2B*	+			(+)	(ALS)

Brackets indicate rare associated genes or unusual phenotypes. *Characteristic pattern of pathology, not the clinical syndrome. ‡Genes in which variation may cause or increase the risk of FTD with the corresponding FTLD pathological subtype. FTLD with no inclusions is not included in this table as no genetic or clinical correlations have been made for this subtype. Abbreviations: aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; BIBD, basophilic inclusion body disease; bvFTD, behavioural variant FTD; *C9orf72*, chromosome 9 open reading frame 72; CBD, corticobasal degeneration; *CHMP2B*, charged multivescicular body protein 2B; FTD, frontotemporal dementia; FTD-3, FTD linked to chromosome 3; FTLD, frontotemporal lobar degeneration; *FUS*, fused in sarcoma; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; MND, motor neuron disease; MSTD, multiple system tauopathy with dementia; NFT, neurofibrillary tangle-predominant; NIFID, neuronal intermediate filament inclusion disease; PiD, Pick disease; PLS, primary lateral sclerosis; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia; *TARDBP* and TDP, TAR DNA-binding protein; UPS, ubiquitin proteasome system; *VCP*, valosin-containing protein; WMT-GGI, white matter tauopathy with globular glial inclusions.

Advances in molecular genetics

GRN variants and progranulin regulators

In less than 6 years, 69 different pathogenic *GRN* mutations have been reported in more than 230 families worldwide, accounting for 5–20% of cases of familial FTD and 1–5% of sporadic cases.[13,43] Progranulin is a multifunctional secreted growth factor that is expressed by many cell types including neurons.[44] Pathogenic mutations in *GRN* are of various types and occur throughout the gene, but all cause disease via haploinsufficiency.[15,16] As a result, substantially reduced levels of progranulin protein are consistently observed in plasma, serum and cerebrospinal fluid samples from symptomatic and asymptomatic *GRN* mutation carriers.[45–47] On the basis of these findings, ELISAs to measure levels of progranulin are being developed as an inexpensive alternative to classic sequencing analyses for diagnostic testing of patients with FTD.

Genetic modifiers and regulators of GRN expression

The clinical phenotype associated with *GRN* mutations is variable[48–53] and penetrance is incomplete.[54] Understanding the factors that modify the expression of *GRN* mutations or regulate the normal *GRN* gene is of potential therapeutic importance. One such genetic factor is variation in the uncharacterized transmembrane protein 106B (*TMEM106B*) gene, which was recently uncovered in a genome-wide association study (GWAS) of patients with known FTLD-TDP pathology.[55] Genetic variants in and near *TMEM106B* seem to protect from—or delay the onset of—FTD in individuals with pathogenic *GRN* mutations, possibly by increasing the levels of progranulin.[55–58] A number of microRNAs, including miR-29b and miR-107, have also been implicated in *GRN* regulation.[59,60] In addition, the minor T allele of genetic variant rs5848 (located in the 3' untranslated region of *GRN*) was found to increase the binding of miR-659 to *GRN*, thereby reducing the levels of progranulin.[61] Genetic association studies have shown that carriers who are homozygous for the T allele of rs5848 have a threefold increased risk of developing FTLD-TDP compared with homozygous C-allele carriers,[61] supporting a role for progranulin in sporadic FTD and possibly other neurodegenerative diseases such as Alzheimer disease.[62–64]

GRN expression may also be modified by exogenous factors. *GRN* transcription was shown to be enhanced by small molecules such as suberoylanilide hydroxamic acid,[65] whereas inhibitors of the vacuolar ATPase, and some alkalizing drugs, increased progranulin production and secretion through a translational mechanism.[66]

Cellular biology of progranulin

Substantial progress has been made in recent years towards our understanding of progranulin biology and the neuroprotective function of this protein. Addition of progranulin to stressed or progranulin-depleted neuronal cells promotes neurite outgrowth.[67–70] The neuroprotective effects of progranulin might be attributable, at least in part, to the activation of cell signalling pathways involved in cell survival,[67,71–74] and a role for progranulin in excitotoxicity and synaptic transmission has also been suggested.[69,75] Importantly, sortilin (SORT1), a receptor for neurotrophic factors in the brain, was identified in two independent studies as the first known receptor for progranulin.[76,77] SORT1 has been shown to mediate progranulin endocytosis and regulate the levels of progranulin *in vivo* in mouse brain and in human plasma. Another study, published in 2011, reported that tumour necrosis factor receptors directly interact with progranulin.[78] The identification of progranulin receptors is exciting, as it opens new avenues in progranulin cell biology research and provides another potential route to FTD therapy.

Box 1 | Timeline of discoveries in the molecular pathogenesis of FTD

- 1892: Arnold Pick describes lobar atrophy in a patient with presenile dementia and aphasia[147]
- 1911: Alois Alzheimer characterizes Pick bodies using silver stains[148]
- 1960s: Descriptions of PSP and CBD clinicopathological syndromes[149,150]
- 1974: Different pathological subtypes of PiD described[151]
- Mid-1980s–early 1990s: Identification of tau as major component of pathological lesions in Alzheimer disease, PiD, PSP and CBD[152]
- 1990: Description of FTD cases without specific histopathology, termed DLDH[153]
- Mid-1990s: Identification of FTLD-U, a subset of FTD with ubiquitin-immunoreactive inclusions[154]
- 1998: Mutations in the microtubule-associated protein tau gene (*MAPT*) identified in some families with FTD and parkinsonism genetically linked to chromosome 17[10–12]
- 2004–2006: Recognition that most cases of DLDH are really FTLD-U, and that FTLD-U is the most common FTD-associated pathology[34]
- 2006: Description of different patterns of FTLD-U that correlate with clinical phenotypes, genetic abnormalities and biochemical properties of inclusions[116,118]
- 2006: Discovery that mutations in the progranulin gene (*GRN*) cause autosomal dominant FTD and explain all remaining chromosome 17-linked families[15,16]
- 2006: TDP-43 identified as pathological protein in most cases of FTLD-U and ALS[35,36]
- 2008: Identification of a subset of FTLD-U cases that lack TDP-43-immunoreactive pathology, termed atypical FTLD-U, or aFTLD-U[155,156]
- 2009: Discovery that most cases of tau-negative and TDP-43-negative FTLD have FUS-immunoreactive pathology (FTLD-FUS)[39–41]
- 2011: Discovery that FTLD-FUS shows accumulation of other FET protein family members TAF15 and EWS[42]
- 2011: FTD and ALS associated with a gene defect on chromosome 9p identified as a repeat expansion in *C9orf72*[28,29]

Abbreviations: ALS, amyotrophic lateral sclerosis; CBD, corticobasal degeneration; DLDH, dementia lacking distinct histopathology; FTD, frontotemporal dementia; FUS, fused in sarcoma; PiD, Pick disease; PSP, progressive supranuclear palsy; TDP-43, TAR DNA-binding protein 43.

C9orf72 mutation

Since 2006, increasing evidence has suggested the presence of a major locus for the combined phenotype of FTD and ALS on chromosome 9p21, but the disease mutation remained elusive (Box 2).[19–27] The key to the identification of the disease-causing mutation was the observation of non-Mendelian inheritance of a GGGGCC hexanucleotide repeat located in a noncoding region of *C9orf72* (Figure 1a) in a large FTD–ALS family designated VSM-20 (Vancouver, San Francisco and Mayo family 20).[28] Using primers that flanked the repeat region, researchers discovered that all affected individuals in this family appeared homozygous by fluorescent PCR, yet affected children did not seem to inherit an allele from their affected parent. This finding suggested the presence

Box 2 | History of the chromosome 9p FTD–ALS locus

Since 2006, at least 10 families with autosomal dominantly inherited FTD, ALS or both have been reported with conclusive or suggestive linkage to chromosome 9p.[19–27] The minimal candidate region shared by all families was a 3.7 Mb region containing only 10 known or predicted genes. In 2010, three GWAS in sporadic ALS populations identified a novel susceptibility locus on chromosome 9p that completely overlapped with the candidate region for familial FTD–ALS.[157–159] The strongest association was found in an ~80 kb haplotype block containing only three genes: *MOBKL2B*, *IFNK* and *C9orf72*. An independent GWAS in patients with pathologically confirmed FTLD-TDP nominated the same chromosomal region, implicating the chromosome 9p gene defect in sporadic forms of both FTD and ALS.[55] However, despite concerted efforts by the FTD and ALS research communities, in-depth candidate-gene sequencing and targeted next-generation sequencing of the minimal candidate region failed to identify the causative mutation, suggesting that a complex mutational mechanism may be involved. In 2011, an expanded hexanucleotide repeat in the noncoding region of *C9orf72* was found to be the long-sought-after cause of FTD and ALS on chromosome 9p.[28,29]

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; GWAS, genome-wide association studies.

of a repeat expansion that was too large to be amplified by the PCR method, a suspicion that was confirmed using a repeat-primed PCR assay (Figure 1b) and Southern blot analysis. The polymorphic nature of this GC-rich hexanucleotide repeat was independently recognized by means of next-generation sequencing in a Welsh family with FTD–ALS,[29] further implying a role for this genomic region in disease pathogenesis.

Mutation frequency

In the 6 months since discovery of the *C9orf72* mutation, numerous FTD and ALS patients have been screened using the repeat-primed PCR assay for the presence of GGGGCC repeat expansions in *C9orf72* (Table 2).[28,29,79–95] Mutation frequency has varied substantially among populations, with the highest frequency observed in genetically isolated populations from Finland and Sardinia, and in cohorts where all patients had a pathological diagnosis of FTLD-TDP (with or without ALS).[28,29,82,86,89] The average mutation frequencies reported in North American and European populations are 37% for familial ALS, 6% for sporadic ALS, 21% for familial FTD, and 6% for sporadic FTD patients. In all series, the *C9orf72* mutation is the most common genetic cause of familial ALS (more frequent than superoxide dismutase 1 mutations) and is comparable in frequency to *GRN* mutations in FTD families. To date, most of the patients included in the mutation screenings have been white; however, *C9orf72* repeat expansions have also been identified in patients of African American, Middle Eastern and Asian race.[87,89,95] Interestingly, independent of clinical presentation or ethnic origin, all *C9orf72* mutation carriers inherit the expansion on the same genetic background, suggesting the presence of a common ancestor or, alternatively, the occurrence of multiple independent expansions on a fragile predisposing disease haplotype.[89,96,97]

Clinical phenotypes

Several groups from North America and Europe have published descriptions of the demographic, clinical and neuropathological features of their cohorts with the *C9orf72* mutation.[28,29,79–95] The clinical presentation of patients with this mutation is heterogeneous and highly variable between and within families. Patients may present with FTD, ALS or features of both. The FTD subtype is most often bvFTD, with PNFA being observed less frequently. ALS typically shows early involvement of both upper and lower motor neurons, and bulbar presentation is particularly common.[80,82,83,95] Several studies have found that ALS patients with the *C9orf72* mutation have a slightly earlier onset and shorter disease duration than those without the mutation.[80,82,83,85,92,95] In addition to FTD and ALS, other features in patients with the mutation can include memory disorder,[79,86,88,91,93,94] psychosis,[79,84,86,93,94] extrapyramidal movement disorder (usually an akinetic–rigid syndrome)[79,83,84,86,91,93] and cerebellar signs.[86] Symptoms tend to accumulate and phenotypes converge with disease progression, with most patients eventually developing some abnormalities of behaviour, language and motor function.[79,81,83,86,95] Wide variation exists in the age at onset (27–83 years, mean ~50 years) and disease duration (1–22 years), and several studies have noted earlier disease onset in subsequent generations, consistent with the phenomenon of genetic anticipation.[79,82,83,85,86,95] Assessment of patients with the *C9orf72* mutation by means of structural neuroimaging tends to show symmetrical bilateral atrophy, primarily affecting frontotemporal regions, but also involving other cerebral lobes and the cerebellum.[79,86,88,93,98]

Neuropathology

The neuropathology associated with the *C9orf72* mutation is a combination of FTLD-TDP and classic ALS.[28,79,80,83,85,86,88,91,93–95,99,100] Regardless of the clinical phenotype, postmortem examination usually shows TDP-43-positive inclusions in a wide range of neuroanatomical regions, including the extramotor cerebral cortex, hippocampus, basal ganglia, substantia nigra, and lower motor neurons of the brainstem and spinal cord. In addition, a unique and highly characteristic feature of patients with the mutation is the presence of neuronal inclusions in the cerebellar granule cell layer, hippocampal pyramidal neurons and other neuroanatomical sites that stain positively for proteins of the ubiquitin proteasome system (such as ubiquitin, ubiquilins and p62) but are negative for TDP-43 (Figure 1c).[28,79,80,83,85,86,88,91,93–95,99,100] This consistent finding suggests that the mutation causes abnormal metabolism and accumulation of one or more as yet unidentified molecules, which could include mutant RNA or RNA-binding proteins, or protein products of aberrant splicing. To date, immunohistochemical studies using commercial antibodies against C9orf72 have failed to demonstrate any abnormal distribution or accumulation of this protein.[28,80,83,86,88,94,95]

Repeat size

All *C9orf72* mutation screenings performed thus far have used the repeat-primed PCR method to detect the presence of a pathogenic GGGGCC repeat expansion. However, it is important to note that this method is only semiquantitative and that the characteristic stutter pattern

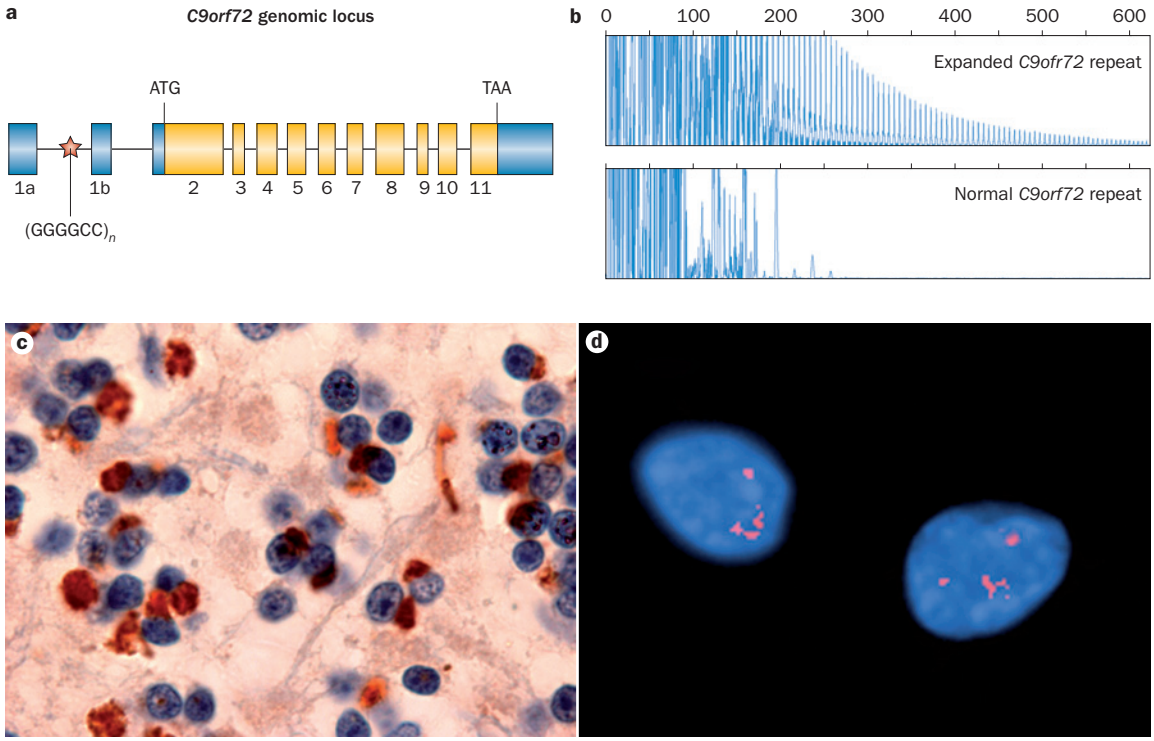

Figure 1 | Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9orf72* causes FTD and ALS linked to chromosome 9p. **a** | Genomic structure of *C9orf72*, showing coding (yellow) and noncoding (blue) exons, the position of the start codon (ATG) and stop codon (TAA), and the $(GGGGCC)_n$ repeat in the intronic region between exons 1a and 1b (star). **b** | PCR products of repeat-primed PCR reactions zoomed to 2,000 relative fluorescence units show stutter amplification in an FTD patient with the pathogenic expanded *C9orf72* repeat (top) and an FTD patient with a normal *C9orf72* repeat length (bottom). **c** | In addition to FTLD-TDP and ALS pathology, all patients with the *C9orf72* mutation show a unique pattern of ubiquitin-positive (brown), TDP-43-negative neuronal inclusions in the cerebellar granule layer and other specific neuroanatomical regions. **d** | RNA foci, visualized using a Cy3-labelled $(GGCCCC)_4$ oligonucleotide probe (red), in the nuclei of two lower motor neurons from a patient with FTD–ALS carrying the expanded GGGGCC repeat in *C9orf72*. Abbreviations: ALS, amyotrophic lateral sclerosis; *C9orf72*, chromosome 9 open reading frame 72; FTD, frontotemporal dementia; TDP, TAR DNA-binding protein.

on PCR (Figure 1b) cannot be used to determine the exact number of repeats. In one family, Southern blot analyses performed using DNA extracted from lymphoblast cell lines showed pathogenic repeat expansions of 700–1,600 repeat units;[28] however, the minimal repeat size required for disease manifestation may be considerably smaller. As in other noncoding repeat expansion disorders, evidence for somatic instability of the *C9orf72* repeat exists.[28] Consequently, repeat lengths may vary among different tissues within the same individual, making it difficult to accurately size the repeat and determine correlations between genetics, clinical presentation and pathology.[101–103]

Combined with the aforementioned technical challenges, our lack of knowledge of the minimal pathogenic repeat size raises important questions regarding genetic testing for this common mutation, particularly in the context of predictive genetic testing. Accurate sizing of the expanded repeat in large FTD and ALS patient series will be crucial to establish a reliable cut-off size, which will assist when counselling individuals who are undergoing genetic testing. Future studies should also determine whether the repeat length contributes to the variability in onset age and clinical presentation, or whether other genetic and/or environmental modifiers are involved.

Disease mechanism

C9orf72 is a completely uncharacterized protein, the function of which is unknown. Two different isoforms of the protein are predicted to be generated from a total of three different *C9orf72* transcripts;[28] however, the relative expression of each of these transcripts in individual brain regions has not been studied. Several groups have shown ~50% loss of at least one *C9orf72* transcript in expanded-repeat carriers, presumably owing to interference of the expanded GC-rich repeat with *C9orf72* transcription regulation.[28,29,85] Although these findings support a possible loss-of-function disease mechanism, the accumulation of transcripts containing the GGGGCC repeat as nuclear RNA foci in the frontal cortex and spinal cord of *C9orf72* mutation carriers has also been demonstrated (Figure 1d), suggesting a possible toxic RNA gain-of-function disease mechanism.[28] On the basis of current knowledge of the pathogenesis of other noncoding repeat expansion disorders, one might suggest that these RNA foci will alter the function of one or more RNA-binding proteins, resulting in downstream changes in gene expression and/or alternative splicing of a range of transcripts.[104] A number of cellular and animal models, involving either elimination of C9orf72 expression or overexpression of

Table 2 | Frequency of the *C9orf72* repeat expansion in FTD and ALS patient populations

Study region*	Familial FTD		Sporadic FTD		Familial ALS		Sporadic ALS		Cases excluded‡
	n	*C9orf72* mutation	*n*	*C9orf72* mutation	*n*	*C9orf72* mutation	*n*	*C9orf72* mutation	
Europe									
Finland[29,89]	27	13 (48.1%)	48	9 (18.8%)	112	52 (46.4%)	289	61 (21.1%)	Yes
Ireland[81]	NA	NA	NA	NA	47	18 (38.3%)	386	19 (4.9%)	NS
UK[83,§]	NA	NA	NA	NA	63	27 (42.9%)	500	35 (7.0%)	No
UK[88,§]	93	12 (12.9%)	163	6 (3.7%)	NA	NA	NA	NA	No
UK[94,§]	161	20 (12.4%)	209	16 (7.7%)	NA	NA	NA	NA	No
Netherlands[89,93]	129	37 (28.7%)	224	5(2.2%)	NA	NA	NA	NA	Yes
Belgium[85,‖]	75	12 (16.0%)	230	9 (3.9%)	15	7 (46.7%)	122	6 (4.9%)	Yes
France[89]	50	22 (44.0%)	150	14 (9.3%)	NA	NA	NA	NA	Yes
Germany[29,82,89]	29	4 (13.8%)	NA	NA	69	15 (21.7%)	421	22 (5.2%)	Yes
Italy (mainland)[29,82,89,92]	NA	NA	NA	NA	120	45 (37.5%)	1,523	55 (3.6%)	Yes
Italy (Sardinia)[82,89,92]	NA	NA	NA	NA	21	12 (57.1%)	133	9 (6.8%)	Yes
Italy (Sicily)[92]	NA	NA	NA	NA	NA	NA	101	5 (4.9%)	Yes
Greece[90]	NA	NA	NA	NA	10	5 (50.0%)	136	11 (8.1%)	NS
North America									
USA[28,79]	171	20 (11.7%)	203	6 (3.0%)	34	8 (23.5%)	195	8 (4.1%)	No
USA[29,89,¶]	NA	NA	NA	NA	163	59 (36.2%)	1014	56 (5.5%)	NS
Canada[95]	NA	NA	NA	NA	62	17 (27.4%)	169	6 (3.6%)	No
Canada[28,86,#]	26	16 (61.5%)	3	0 (0.0%)	NA	NA	NA	NA	No
USA[28,#]	40	9 (22.5%)	53**	8 (15.1%)	NA	NA	NA	NA	No
USA[80,#]	18	6 (33.3%)	6	0 (0.0%)	14	6 (42.9%)	43**	5 (11.6%)	NS
Other regions									
Israel[89]	NA	NA	NA	NA	14	3 (21.4%)	NA	NA	NS
India[89]	NA	NA	31	0 (0.0%)	NA	NA	31	0 (0.0%)	NS
Asia[89,‡‡]	3	2 (66.7%)	10	0 (0.0%)	20	1 (5.0%)	238	0 (0.0%)	NS
Guam[89]	NA	NA	NA	NA	NA	NA	90	0 (0.0%)	NS
Australia[89]	NA	NA	NA	NA	NA	NA	263	14 (5.3%)	NS

*Only geographical regions with at least 10 FTD or ALS patients are listed. ‡In studies in which patients known to carry mutations in other genes were excluded, the frequency of *C9orf72* repeat expansions are overestimated. §Cohorts are part of a larger series of UK patients which are grouped in Majounie *et al.*[89] with highly comparable mutation frequencies. ‖Numbers do not include 23 patients with both FTD and ALS, of which 85.7% of familial and 6.3% of sporadic patients were *C9orf72* mutation carriers. ¶In the sporadic ALS cohort, 5.4% (48 of 890) of white patients and 4.1% (2 of 49) of African American patients carried a *C9orf72* repeat expansion. #Only included patients with a pathological diagnosis of FTLD-TDP. ** Includes individuals for whom no information on family history was available. ‡‡The geographical origin of the Asian patients was not reported in detail; however, the familial ALS patient carrying the *C9orf72* repeat expansion was Japanese. Abbreviations: ALS, amyotrophic lateral sclerosis; *C9orf72*, chromosome 9 open reading frame 72; FTD, frontotemporal dementia; NA, not applicable; NS, not stated.

human *C9orf72* containing expanded GGGGCC repeats, are currently being generated to determine the contribution of each disease mechanism to neurodegeneration and TDP-43 aggregation.

Other genes and genetic risk factors

FTD-related genes

With the identification of the repeat expansion in *C9orf72*, we have now accounted for all previously published FTD families with genome-wide linkage. Although it is unlikely that any other common FTD-related genes exist, rare mutations in other genes could explain a small number of the remaining families. Combinations of genetic variants and environmental factors are likely to be responsible for disease in the majority of patients with sporadic FTD. The use of whole-exome sequencing and whole-genome sequencing will greatly facilitate the discovery of rare genetic defects in the future, as was recently demonstrated with the identification of mutations in the colony stimulating factor 1 receptor gene as the cause of hereditary diffuse leukoencephalopathy with spheroids,[105] a disorder with variable clinical presentation that includes features of FTD. Additional GWAS—such as a large collaborative study that is currently underway, which includes more than 2,500 samples from patients with FTD—may identify additional genetic risk factors.

ALS-related genes

Other rare genetic causes of FTD that have been identified in recent years include *TARDBP* and *FUS*, although

mutations in each of these genes usually cause a pure ALS phenotype.[37,38,106,107] In 2011, *UBQLN2*, a gene that encodes a member of the ubiquilin family, which is involved in the degradation of ubiquitinated proteins, was also added to the list of ALS–FTD-related genes.[108] Progressive dementia with abnormalities in both behaviour and executive functions were reported in ~20% of *UBQLN2* mutation carriers; however, none of these patients presented with FTD alone.

Advances in molecular pathology

TDP-43

TDP-43 is a highly conserved, predominantly nuclear protein that can shuttle between the nucleus and cytoplasm. This protein has a number of well-described functions in RNA regulation, such as the control of splicing, and in mRNA transport and stability; however, the full complexity of TDP-43 function is only just emerging.[109–111]

FTLD-TDP

Abnormal accumulation of TDP-43 in neuronal and glial inclusions is the characteristic neuropathological feature in ~50% of patients with FTD (a condition termed FTLD-TDP) and in the vast majority of ALS cases.[31,35,36] Pathological modifications of TDP-43 in these disorders include a redistribution of the protein from the nucleus to the cytoplasm in cells with inclusions, as well as hyperphosphorylation, ubiquitination and N-terminal truncation of the protein.[36] FTLD-TDP includes sporadic and genetic forms, with mutations having been identified in *GRN*, *VCP* and *TARDBP*, along with the recently recognized *C9orf72* repeat expansion (as described above).[28,29,112–115] On the basis of the morphology and anatomical distribution of TDP-43 pathology, four distinct FTLD-TDP subtypes can be recognized.[116–118] The relevance of this heterogeneity is supported by clinical and genetic correlations (Table 1), as well as by emerging evidence for distinct biochemical properties of TDP-43 in the different subtypes.[36,118,119]

Pathogenesis of TDP-43 proteinopathies

The neuropathological findings in patients with FTLD-TDP implicate both loss-of-function and gain-of-function mechanisms in TDP-43-associated cell death. Numerous research groups worldwide are focused on addressing these mechanisms, and detailed discussions of TDP-43 pathogenesis have been published elsewhere.[120–122] Briefly, current *in vivo* models provide evidence for both scenarios: neither reduced nor increased expression of the tightly autoregulated TDP-43 protein is well-tolerated.[120–122] However, no model has fully recapitulated the neuropathological and biochemical features of human TDP-43 related diseases. Although the presence of *TARDBP* mutations is a clear indicator that dysfunction of TDP-43 is directly linked to neurodegeneration, the functional consequences of *TARDBP* mutations are still unresolved. No solid evidence that *TARDBP* mutations act through a toxic gain-of-function mechanism exists, and no functional consequences of *TARDBP* mutations on the processing of selected RNA targets have been reported. However, studies that used crosslinking immunoprecipitation and high-throughput sequencing have identified more than 6,000 RNA targets of TDP-43.[110,111] A major challenge is to dissect the

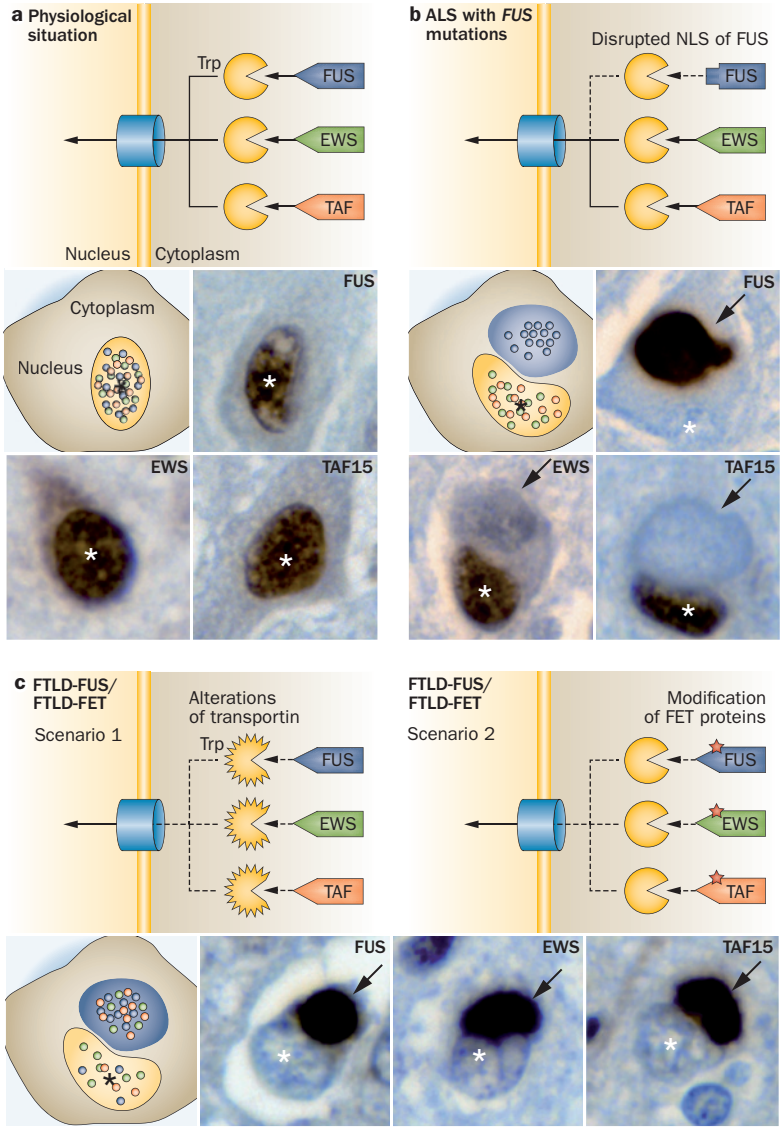

Figure 2 | Distinct pathomechanisms of ALS-*FUS* and FTLD-FUS. The FET protein family members FUS (blue), EWS (green) and TAF15 (red) all contain a proline–tyrosine NLS (represented as a triangle) that binds to the receptor protein Trp, which mediates the transport of these proteins into the nucleus. **a** | Under physiological conditions, the FET proteins bind normally to Trp (top panel), and all have predominantly nuclear localization (bottom panels). **b** | In ALS-*FUS*, the NLS of FUS is disrupted owing to mutations (rectangle), leading to impaired interaction with Trp and lack of nuclear import of FUS. Consequently, FUS accumulates as a cytoplasmic inclusion, with normal nuclear transport of TAF15 and EWS (bottom panels). **c** | Patients with FTLD-FUS/FTLD-FET show co-accumulation of all FET proteins in cytoplasmic inclusions (bottom images), which may be explained by either of two broad scenarios: alterations of Trp itself, such as by genetic variations, reduced expression levels or post-translational modifications (scenario 1), or post-translational modifications of FET proteins with altered Trp binding (scenario 2). All photomicrographs show a single neuron with a cytoplasmic inclusion (arrow) and nucleus (asterisk), immunostained for the indicated FET protein (brown stain). Abbreviations: ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; NLS, nuclear localization signal; Trp, transportin-1.

individual pathways that are regulated by TDP-43, and to identify possible disease-relevant RNA targets.

Another important but unresolved issue is the role of TDP-43 in the non-*TARDBP*-associated genetic forms of FTLD-TDP. The fact that disease associated with mutations in *GRN*, *VCP* or *C9orf72* is consistently characterized by the presence of TDP-43 pathology suggests that dysregulation of TDP-43 might be a crucial common downstream mechanism leading to cell death in each of these disorders. However, the relevance of TDP-43 accumulation in *C9orf72* mutation carriers has recently been challenged by the identification of TDP-43-negative, ubiquitin-positive pathology that is more abundant than the TDP-43 pathology in distinct brain regions (Figure 1c), raising the possibility that, in these cases, another unidentified protein—or proteins—might be more important than TDP-43 in the pathogenesis.[28,79,80,83,85,86,88,91,93–95,99,100]

FUS and other FET proteins

FUS belongs to the FET protein family, which also includes EWS, TAF15, and the *Drosophila* orthologue of FUS, Cabeza. These proteins are highly conserved, ubiquitously expressed, predominantly nuclear (Figure 2a), multifunctional DNA/RNA-binding proteins[123] that can bind to a large number of partially overlapping RNA targets.[124]

FTLD-FUS

Early in 2009, *FUS* mutations were reported to be the cause of ~3% of familial ALS cases in which the associated pathology was characterized by FUS-positive, TDP-43-negative inclusions.[37,38] These cases were consequently termed ALS-*FUS*. Subsequently, FUS was found to be the most characteristic marker for the pathology in many of the remaining tau/TDP-negative FTLD cases, which include three closely related but distinct clinicopathological entities: atypical FTLD-U (aFTLD-U), neuronal intermediate filament inclusion disease, and basophilic inclusion body disease.[39–41,125] The identification of FTLD-FUS as a new molecular subgroup[32] provided further evidence that FTD and ALS are closely related conditions, and emphasized the pathogenic role of RNA-binding proteins in these disorders. However, despite some overlap in the phenotype and pathological features of FTLD-FUS and ALS-*FUS*, marked differences were also observed.[126,127] Moreover, after additional cases were reported, it became evident that ALS with FUS pathology is almost always caused by a *FUS* mutation, whereas cases of FTLD-FUS tend to be sporadic, with none yet associated with a genetic abnormality of *FUS*.[39–41,125]

Further evidence for different pathomechanisms in the two disorders was provided via a study that investigated FET protein members (other than FUS) in a series of ALS-*FUS* and FTLD-FUS cases.[42] In ALS-*FUS* with a range of different mutations, no co-accumulation of other FET proteins into FUS-positive inclusions was found, with only nuclear staining of TAF15 and EWS being observed (Figure 2b). In striking contrast, in all FTLD-FUS subtypes, TAF15 and EWS were found to co-accumulate in FUS-positive cytoplasmic inclusions, and inclusion-bearing cells showed reduced levels of nuclear staining of all three FET proteins, particularly TAF15 (Figure 2c).

The addition of TAF15 and EWS to the growing list of neurodegeneration-associated RNA-binding proteins is further supported by studies in which TAF15 was identified as a candidate through a yeast functional screen to identify RNA binding proteins with similar function to TDP-43 and FUS.[128] Descriptions of genetic variants (of undetermined pathogenic relevance) in *TAF15* and *EWSR1* in a small number of ALS cases provide further evidence for a role for these proteins in neurodegeneration.[129,130] Although the roles of FUS, TAF15 and EWS in FTLD-FUS remains to be elucidated, the term FTLD-FET now seems more appropriate for this molecular FTLD subgroup.

Pathogenesis of FUS proteinopathies

The differences in the molecular pathology of ALS-*FUS* and FTLD-FUS imply that different pathological processes underlie inclusion formation and cell death in each disorder: ALS-*FUS* might be restricted to dysfunction of FUS, whereas FTLD-FUS may involve dysfunction of all FET proteins (Figure 2).

In ALS-*FUS,* mutations in the C-terminus of the FUS protein disrupt a region characterized as a nonclassical nuclear localization sequence. This disruption leads to impaired transportin-mediated nuclear import of FUS, with redistribution of the protein to the cytoplasm (Figure 2b).[131,132] Importantly, localization of other FET proteins is not altered under these conditions.[42] The degree of impairment in FUS nuclear transport varies among different *FUS* mutations, but correlates with the observed variability in disease course associated with different mutations, and with distinct pathological patterns of ALS-*FUS* pathology.[126] This finding provides strong evidence that impaired nuclear import of FUS is a key event in ALS-*FUS* disease pathogenesis.

In FTLD-FUS, a more general defect of transportin-mediated nuclear import that affects the distribution of all FET proteins is postulated, with two plausible scenarios (Figure 2c). First, a primary defect of transportin itself, resulting either from genetic variations in the transportin gene (*TNPO1*) or from post-translational modifications or altered expression levels of transportin protein, could lead to reduced efficiency of nuclear import of all FET proteins. In this scenario, however, one might also expect alterations in the subcellular distribution of other transportin cargos such as hnRNPA1, which has not been supported by preliminary data.[42] Second, the normal nuclear import of FET proteins might be affected by abnormal post-translational modifications of FET proteins, such as arginine methylation or phosphorylation, which have been shown to modulate nucleocytoplasmic transport, protein–protein interaction and protein stability.[123,133–139] So far, biochemical analysis of protein extracted from FTLD-FUS brains has revealed increased insolubility of all FET proteins, without other obvious disease-associated changes such as truncation or abnormal phosphorylation;[40,42,140] however, more-detailed biochemical analyses are required.

The downstream effects of redistribution of FUS or all FET proteins in the pathogenesis of ALS-*FUS* and

FTLD-FUS, respectively, have not been determined. As in the case of TDP-43, either a gain of toxic properties or a loss of function owing to sequestration of these proteins in aggregates is plausible. Results from initial *in vivo* models of ALS-*FUS* have been inconsistent and the mechanisms remain unresolved.[122,141]

Molecular correlates of FTD phenotypes

Each of the molecular subtypes of FTLD pathology is associated with a range of clinical features and may be caused by defects in specific genes (Table 1). However, prediction of the underlying molecular pathology or genetics on the basis of pattern of inheritance and clinical features is often imprecise.[142,143] Semantic dementia is usually sporadic and associated with FTLD-TDP type C, with fewer cases having the pathology of classical Pick disease. Cases of sporadic PNFA are more likely to have FTLD-tau than FTLD-TDP, but bvFTD can be associated with any of the major pathologies. Early-onset bvFTD with severe psychobehavioural abnormality, but with minimal motor features or aphasia, is characteristic of the aFTLD-U subtype of FTLD-FUS. When FTD is combined with ALS, the pathology is usually FTLD-TDP, whereas FTD with prominent parkinsonism is more often FTLD-tau (namely, progressive supranuclear palsy or corticobasal degeneration). In families with autosomal dominant inheritance of bvFTD or PNFA without marked motor dysfunction, the underlying gene defect may be a mutation in *C9orf72*, *GRN* or *MAPT*. When parkinsonism or primary lateral sclerosis are also prominent features, a *MAPT* mutation is more likely, whereas coexistence of classical ALS in a family strongly suggests a *C9orf72* mutation. Further research is required to improve our understanding of the correlation between molecular basis and clinical phenotypes of the different FTD subgroups.

Conclusions and future directions

The past 6 years have seen remarkable progress in our understanding of the molecular basis of FTD. Apparently, all common FTD-causing genes have now been discovered and the major pathological proteins identified. Although many aspects of specific pathogenic mechanisms remain to be resolved, we are already in a position to begin translating this newly acquired knowledge into improved patient care. The recent discoveries of mutations in *GRN* and *C9orf72* will enable more-informed genetic counselling, and our improved knowledge of the pathological proteins in FTD is driving attempts to develop disease-specific, molecular-based diagnostic tests, such as the quantification of total or pathological protein species in biofluids.[144,145] Recognition of progranulin insufficiency as an important pathomechanism in familial FTD and some sporadic forms of FTD, combined with improved understanding of progranulin regulation and cell biology, has already led to initial plans for progranulin-based clinical trials.[146] The identification of a role for TDP-43, FET proteins and *C9orf72* in FTD has opened up new avenues of research related to RNA regulation. Finally, a greater appreciation of the overlap between FTD and ALS is now bringing research and patient care in these disorders closer together. Hopefully, patients with FTD will soon experience real benefits from these and future advances.

Review criteria

References for this Review were identified by searching PubMed using the terms "frontotemporal dementia", "frontotemporal lobar degeneration", "progranulin", "TDP-43", "FUS", "FET", "C9orf72", "genetics", "molecular" and "pathology". Only articles published in English from 2006 to April 2012 were reviewed. Additional papers were identified from the reference lists of identified articles.

1. Bird, T. *et al.* Epidemiology and genetics of frontotemporal dementia/Pick's disease. *Ann. Neurol.* **54** (Suppl. 5), S29–S31 (2003).
2. Feldman, H. *et al.* A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. *Neuroepidemiology* **22**, 265–274 (2003).
3. [No authors listed] Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J. Neurol. Neurosurg. Psychiatry* **57**, 416–418 (1994).
4. McKhann, G. M. *et al.* Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch. Neurol.* **58**, 1803–1809 (2001).
5. Neary, D. *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**, 1546–1554 (1998).
6. Burrell, J. R., Kiernan, M. C., Vucic, S. & Hodges, J. R. Motor neuron dysfunction in frontotemporal dementia. *Brain* **134**, 2582–2594 (2011).
7. Lomen-Hoerth, C., Anderson, T. & Miller, B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* **59**, 1077–1079 (2002).
8. Rohrer, J. D. *et al.* The heritability and genetics of frontotemporal lobar degeneration. *Neurology* **73**, 1451–1456 (2009).
9. Seelaar, H. *et al.* Distinct genetic forms of frontotemporal dementia. *Neurology* **71**, 1220–1226 (2008).
10. Hutton, M. *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702–705 (1998).
11. Poorkaj, P. *et al.* Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann. Neurol.* **43**, 815–825 (1998).
12. Spillantini, M. G. *et al.* Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc. Natl Acad. Sci. USA* **95**, 7737–7741 (1998).
13. Alzheimer Disease & Frontotemporal Dementia Mutation Database [online], http://www.molgen.ua.ac.be/ftdmutations (2012).
14. Rademakers, R., Cruts, M. & van Broeckhoven, C. The role of tau (*MAPT*) in frontotemporal dementia and related tauopathies. *Hum. Mutat.* **24**, 277–295 (2004).
15. Baker, M. *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* **442**, 916–919 (2006).
16. Cruts, M. *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* **442**, 920–924 (2006).
17. Watts, G. D. *et al.* Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat. Genet.* **36**, 377–381 (2004).
18. Skibinski, G. *et al.* Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat. Genet.* **37**, 806–808 (2005).
19. Boxer, A. L. *et al.* Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family. *J. Neurol. Neurosurg. Psychiatr.* **82**, 196–203 (2011).
20. Gijselinck, I. *et al.* Identification of 2 loci at chromosomes 9 and 14 in a multiplex family with frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Arch. Neurol.* **67**, 606–616 (2010).
21. Le Ber, I. *et al.* Chromosome 9p-linked families with frontotemporal dementia associated with motor neuron disease. *Neurology* **72**, 1669–1676 (2009).
22. Luty, A. A. *et al.* Pedigree with frontotemporal lobar degeneration—motor neuron disease and Tar DNA binding protein-43 positive neuropathology: genetic linkage to chromosome 9. *BMC Neurol.* **8**, 32 (2008).
23. Momeni, P. *et al.* Analysis of *IFT74* as a candidate gene for chromosome 9p-linked ALS–FTD. *BMC Neurol.* **6**, 44 (2006).
24. Morita, M. *et al.* A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* **66**, 839–844 (2006).

25. Pearson, J. P. *et al.* Familial frontotemporal dementia with amyotrophic lateral sclerosis and a shared haplotype on chromosome 9p. *J. Neurol.* **258**, 647–655 (2011).
26. Valdmanis, P. N. *et al.* Three families with amyotrophic lateral sclerosis and frontotemporal dementia with evidence of linkage to chromosome 9p. *Arch. Neurol.* **64**, 240–245 (2007).
27. Vance, C. *et al.* Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–21.3. *Brain* **129**, 868–876 (2006).
28. DeJesus-Hernandez, M. *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* **72**, 245–256 (2011).
29. Renton, A. E. *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS–FTD. *Neuron* **72**, 257–268 (2011).
30. Cairns, N. J. *et al.* Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol.* **114**, 5–22 (2007).
31. Mackenzie, I. R. *et al.* Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol.* **117**, 15–18 (2009).
32. Mackenzie, I. R. *et al.* Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol.* **119**, 1–4 (2010).
33. Lipton, A. M., White, C. L. 3rd & Bigio, E. H. Frontotemporal lobar degeneration with motor neuron disease-type inclusions predominates in 76 cases of frontotemporal degeneration. *Acta Neuropathol.* **108**, 379–385 (2004).
34. Mackenzie, I. R. *et al.* Dementia lacking distinctive histology (DLDH) revisited. *Acta Neuropathol.* **112**, 551–559 (2006).
35. Arai, T. *et al.* TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem. Biophys. Res. Commun.* **351**, 602–611 (2006).
36. Neumann, M. *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* **314**, 130–133 (2006).
37. Kwiatkowski, T. J. Jr *et al.* Mutations in the *FUS/TLS* gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* **323**, 1205–1208 (2009).
38. Vance, C. *et al.* Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science* **323**, 1208–1211 (2009).
39. Munoz, D. G. *et al.* FUS pathology in basophilic inclusion body disease. *Acta Neuropathol.* **118**, 617–627 (2009).
40. Neumann, M. *et al.* A new subtype of frontotemporal lobar degeneration with FUS pathology. *Brain* **132**, 2922–2931 (2009).
41. Neumann, M. *et al.* Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease. *Acta Neuropathol.* **118**, 605–616 (2009).
42. Neumann, M. *et al.* FET proteins TAF15 and EWS are selective markers that distinguish FTLD with FUS pathology from amyotrophic lateral sclerosis with FUS mutations. *Brain* **134**, 2595–2609 (2011).
43. Gijselinck, I., Van Broeckhoven, C. & Cruts, M. Granulin mutations associated with frontotemporal lobar degeneration and related disorders: an update. *Hum. Mutat.* **29**, 1373–1386 (2008).
44. Bateman, A. & Bennett, H. P. The granulin gene family: from cancer to dementia. *Bioessays* **31**, 1245–1254 (2009).
45. Finch, N. *et al.* Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. *Brain* **132**, 583–591 (2009).
46. Ghidoni, R., Benussi, L., Glionna, M., Franzoni, M. & Binetti, G. Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. *Neurology* **71**, 1235–1239 (2008).
47. Sleegers, K. *et al.* Serum biomarker for progranulin-associated frontotemporal lobar degeneration. *Ann. Neurol.* **65**, 603–609 (2009).
48. Beck, J. *et al.* A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. *Brain* **131**, 706–720 (2008).
49. Gass, J. *et al.* Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Hum. Mol. Genet.* **15**, 2988–3001 (2006).
50. Le Ber, I. *et al.* Progranulin null mutations in both sporadic and familial frontotemporal dementia. *Human. Mut.* **28**, 846–855 (2007).
51. Moreno, F. *et al.* "Frontotemporoparietal" dementia: clinical phenotype associated with the c.709-1G>A *PGRN* mutation. *Neurology* **73**, 1367–1374 (2009).
52. Snowden, J. S. *et al.* Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. *Brain* **129**, 3091–3102 (2006).
53. Masellis, M. *et al.* Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain* **129**, 3115–3123 (2006).
54. Cruts, M. & Van Broeckhoven, C. Loss of progranulin function in frontotemporal lobar degeneration. *Trends Genet.* **24**, 186–194 (2008).
55. Van Deerlin, V. M. *et al.* Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nat. Genet.* **42**, 234–239 (2010).
56. Cruchaga, C. *et al.* Association of *TMEM106B* gene polymorphism with age at onset in granulin mutation carriers and plasma granulin protein levels. *Arch. Neurol.* **68**, 581–586 (2011).
57. Finch, N. *et al. TMEM106B* regulates progranulin levels and the penetrance of FTLD in *GRN* mutation carriers. *Neurology* **76**, 467–474 (2011).
58. van der Zee, J. *et al. TMEM106B* is associated with frontotemporal lobar degeneration in a clinically diagnosed patient cohort. *Brain* **134**, 808–815 (2011).
59. Jiao, J., Herl, L. D., Farese, R. V. & Gao, F. B. MicroRNA-29b regulates the expression level of human progranulin, a secreted glycoprotein implicated in frontotemporal dementia. *PLoS ONE* **5**, e10551 (2010).
60. Wang, W. X. *et al.* miR-107 regulates granulin/progranulin with implications for traumatic brain injury and neurodegenerative disease. *Am. J. Pathol.* **177**, 334–345 (2010).
61. Rademakers, R. *et al.* Common variation in the miR-659 binding-site of *GRN* is a major risk factor for TDP43-positive frontotemporal dementia. *Hum. Mol. Genet.* **17**, 3631–3642 (2008).
62. Brouwers, N. *et al.* Genetic variability in progranulin contributes to risk for clinically diagnosed Alzheimer disease. *Neurology* **71**, 656–664 (2008).
63. Lee, M. J., Chen, T. F., Cheng, T. W. & Chiu, M. J. rs5848 variant of progranulin gene is a risk of Alzheimer's disease in the Taiwanese population. *Neurodegener. Dis.* **8**, 216–220 (2011).
64. Viswanathan, J. *et al.* An association study between granulin gene polymorphisms and Alzheimer's disease in Finnish population. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **150B**, 747–750 (2009).
65. Cenik, B. *et al.* Suberoylanilide hydroxamic acid (vorinostat) up-regulates progranulin transcription: rational therapeutic approach to frontotemporal dementia. *J. Biol. Chem.* **286**, 16101–16108 (2011).
66. Capell, A. *et al.* Rescue of progranulin deficiency associated with frontotemporal lobar degeneration by alkalizing reagents and inhibition of vacuolar ATPase. *J. Neurosci.* **31**, 1885–1894 (2011).
67. Gao, X. *et al.* Progranulin promotes neurite outgrowth and neuronal differentiation by regulating GSK-3β. *Protein Cell* **1**, 552–562 (2010).
68. Ryan, C. L. *et al.* Progranulin is expressed within motor neurons and promotes neuronal cell survival. *BMC Neurosci.* **10**, 130 (2009).
69. Tapia, L. *et al.* Progranulin deficiency decreases gross neural connectivity but enhances transmission at individual synapses. *J. Neurosci.* **31**, 11126–11132 (2011).
70. Van Damme, P. *et al.* Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. *J. Cell. Biol.* **181**, 37–41 (2008).
71. Kleinberger, G. *et al.* Increased caspase activation and decreased TDP-43 solubility in progranulin knockout cortical cultures. *J. Neurochem.* **115**, 735–747 (2010).
72. Nedachi, T., Kawai, T., Matsuwaki, T., Yamanouchi, K. & Nishihara, M. Progranulin enhances neural progenitor cell proliferation through glycogen synthase kinase 3β phosphorylation. *Neuroscience* **185**, 106–115 (2011).
73. Rosen, E. Y. *et al.* Functional genomic analyses identify pathways dysregulated by progranulin deficiency, implicating Wnt signaling. *Neuron* **71**, 1030–1042 (2011).
74. Xu, J. *et al.* Extracellular progranulin protects cortical neurons from toxic insults by activating survival signaling. *Neurobiol. Aging* **32**, 2326.e5–2326.e16 (2011).
75. Guo, A., Tapia, L., Bamji, S. X., Cynader, M. S. & Jia, W. Progranulin deficiency leads to enhanced cell vulnerability and TDP-43 translocation in primary neuronal cultures. *Brain Res.* **1366**, 1–8 (2010).
76. Carrasquillo, M. M. *et al.* Genome-wide screen identifies rs646776 near sortilin as a regulator of progranulin levels in human plasma. *Am. J. Hum. Genet.* **87**, 890–897 (2010).
77. Hu, F. *et al.* Sortilin-mediated endocytosis determines levels of the frontotemporal dementia protein, progranulin. *Neuron* **68**, 654–667 (2010).
78. Tang, W. *et al.* The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. *Science* **332**, 478–484 (2011).
79. Boeve, B. F. *et al.* Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in *C9ORF72*. *Brain* **135**, 765–783 (2012).
80. Brettschneider, J. *et al.* Pattern of ubiquilin pathology in ALS and FTLD indicates presence of *C9ORF72* hexanucleotide expansion. *Acta Neuropathol.* **123**, 825–839 (2012).
81. Byrne, S. *et al.* Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a *C9orf72* repeat expansion: a population-based cohort study. *Lancet Neurol.* **11**, 232–240 (2012).

82. Chio, A. *et al.* Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of *C9ORF72*. *Brain* **135**, 784–793 (2012).
83. Cooper-Knock, J. *et al.* Clinico-pathological features in amyotrophic lateral sclerosis with expansions in *C9ORF72*. *Brain* **135**, 751–764 (2012).
84. Floris, G. *et al.* Frontotemporal dementia with psychosis, parkinsonism, visuo-spatial dysfunction, upper motor neuron involvement associated to expansion of *C9ORF72*: a peculiar phenotype? *J. Neurol.* http://dx.doi.org/10.1007/s00415-012-6444-3.
85. Gijselinck, I. *et al.* A *C9orf72* promoter repeat expansion in a Flanders–Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurol.* **11**, 54–65 (2012).
86. Hsiung, G. Y. *et al.* Clinical and pathological features of familial frontotemporal dementia caused by *C9ORF72* mutation on chromosome 9p. *Brain* **135**, 709–722 (2012).
87. Kandiah, N. *et al.* Case report of an Asian patient with FTD–ALS due to *C9ORF72* mutation. *Can. J. Neurol. Sci.* (in press).
88. Mahoney, C. J. *et al.* Frontotemporal dementia with the *C9ORF72* hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain* **135**, 736–750 (2012).
89. Majounie, E. *et al.* Frequency of the *C9orf72* hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* **11**, 323–330 (2012).
90. Mok, K. Y. *et al.* High frequency of the expanded *C9ORF72* hexanucleotide repeat in familial and sporadic Greek ALS patients. *Neurobiol. Aging* http://dx.doi.org/10.1016/j.neurobiolaging.2012.02.021.
91. Murray, M. E. *et al.* Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in *C9ORF72*. *Acta Neuropathol.* **122**, 673–690 (2011).
92. Sabatelli, M. *et al. C9ORF72* hexanucleotide repeat expansions in the Italian sporadic ALS population. *Neurobiol. Aging* http://dx.doi.org/10.1016/j.neurobiolaging.2012.02.011.
93. Simon-Sanchez, J. *et al.* The clinical and pathological phenotype of *C9ORF72* hexanucleotide repeat expansions. *Brain* **135**, 723–735 (2012).
94. Snowden, J. S. *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* **135**, 693–708 (2012).
95. Stewart, H. *et al.* Clinical and pathological features of amyotrophic lateral sclerosis caused by mutation in the *C9ORF72* gene on chromosome 9p. *Acta Neuropathol.* **123**, 409–417 (2012).
96. Mok, K. *et al.* Chromosome 9 ALS and FTD locus is probably derived from a single founder. *Neurobiol. Aging* **33**, 209.e3–209.e8 (2012).
97. Rademakers, R. *C9orf72* repeat expansions in patients with ALS and FTD. *Lancet Neurol.* **11**, 297–298 (2012).
98. Whitwell, J. L. *et al.* Neuroimaging signatures of frontotemporal dementia genetics: *C9ORF72*, tau, progranulin and sporadics. *Brain* **135**, 794–806 (2012).
99. Al-Sarraj, S. *et al.* p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of *C9orf72*-linked FTLD and MND/ALS. *Acta Neuropathol.* **122**, 691–702 (2011).
100. Troakes, C. *et al.* An MND/ALS phenotype associated with *C9orf72* repeat expansion: abundant p62-positive, TDP-43-negative inclusions in cerebral cortex, hippocampus and cerebellum but without associated cognitive decline. *Neuropathology* http://dx.doi.org/10.1111/j.1440-1789.2011.01286.x.
101. Lavedan, C. *et al.* Myotonic dystrophy: size- and sex-dependent dynamics of CTG meiotic instability, and somatic mosaicism. *Am. J. Hum. Genet.* **52**, 875–883 (1993).
102. Matsuura, T. *et al.* Somatic and germline instability of the ATTCT repeat in spinocerebellar ataxia type 10. *Am. J. Hum. Genet.* **74**, 1216–1224 (2004).
103. Moseley, M. L. *et al.* SCA8 CTG repeat: *en masse* contractions in sperm and intergenerational sequence changes may play a role in reduced penetrance. *Hum. Mol. Genet.* **9**, 2125–2130 (2000).
104. Renoux, A. J. & Todd, P. K. Neurodegeneration the RNA way. *Prog. Neurobiol.* **97**, 173–189 (2011).
105. Rademakers, R. *et al.* Mutations in the colony stimulating factor 1 receptor (*CSF1R*) gene cause hereditary diffuse leukoencephalopathy with spheroids. *Nat. Genet.* **44**, 200–205 (2012).
106. Kabashi, E. *et al.* Gain and loss of function of ALS-related mutations of *TARDBP* (TDP-43) cause motor deficits *in vivo*. *Hum. Mol. Genet.* **19**, 671–683 (2010).
107. Sreedharan, J. *et al.* TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* **319**, 1668–1672 (2008).
108. Deng, H. X. *et al.* Mutations in *UBQLN2* cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. *Nature* **477**, 211–215 (2011).
109. Buratti, E. & Baralle, F. E. The multiple roles of TDP-43 in pre-mRNA processing and gene expression regulation. *RNA Biol.* **7**, 420–429 (2010).
110. Polymenidou, M. *et al.* Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. *Nat. Neurosci.* **14**, 459–468 (2011).
111. Tollervey, J. R. *et al.* Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. *Nat. Neurosci.* **14**, 452–458 (2011).
112. Van Deerlin, V. M. *et al. TARDBP* mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. *Lancet Neurol.* **7**, 409–416 (2008).
113. Kovacs, G. G. *et al. TARDBP* variation associated with frontotemporal dementia, supranuclear gaze palsy, and chorea. *Mov. Disord.* **24**, 1843–1847 (2009).
114. Neumann, M. *et al.* TDP-43 in the ubiquitin pathology of frontotemporal dementia with *VCP* gene mutations. *J. Neuropathol. Exp. Neurol.* **66**, 152–157 (2007).
115. Cairns, N. J. *et al.* TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. *Am. J. Pathol.* **171**, 227–240 (2007).
116. Mackenzie, I. R. *et al.* Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. *Acta Neuropathol.* **112**, 539–549 (2006).
117. Mackenzie, I. R. *et al.* A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol.* **122**, 111–113 (2011).
118. Sampathu, D. M. *et al.* Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. *Am. J. Pathol.* **169**, 1343–1352 (2006).
119. Hasegawa, M. *et al.* Molecular dissection of TDP-43 proteinopathies. *J. Mol. Neurosci.* **45**, 480–485 (2011).
120. Lee, E. B., Lee, V. M. & Trojanowski, J. Q. Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nat. Rev. Neurosci.* **13**, 38–50 (2012).
121. Mackenzie, I. R., Rademakers, R. & Neumann, M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Lancet Neurol.* **9**, 995–1007 (2010).
122. Da Cruz, S. & Cleveland, D. W. Understanding the role of TDP-43 and FUS/TLS in ALS and beyond. *Curr. Opin. Neurobiol.* **21**, 904–919 (2011).
123. Tan, A. Y. & Manley, J. L. The TET family of proteins: functions and roles in disease. *J. Mol. Cell Biol.* **1**, 82–92 (2009).
124. Hoell, J. I. *et al.* RNA targets of wild-type and mutant FET family proteins. *Nat. Struct. Mol. Biol.* **18**, 1428–1431 (2011).
125. Urwin, H. *et al.* FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. *Acta Neuropathol.* **120**, 33–41 (2010).
126. Mackenzie, I. R. *et al.* Pathological heterogeneity in amyotrophic lateral sclerosis with FUS mutations: two distinct patterns correlating with disease severity and mutation. *Acta Neuropathol.* **122**, 87–98 (2011).
127. Mackenzie, I. R. *et al.* Distinct pathological subtypes of FTLD-FUS. *Acta Neuropathol.* **121**, 207–218 (2011).
128. Couthouis, J. *et al.* A yeast functional screen predicts new candidate ALS disease genes. *Proc. Natl Acad. Sci. USA* **108**, 20881–20890 (2011).
129. Couthouis, J. *et al.* Evaluating the role of the FUS/TLS-related gene *EWSR1* in amyotrophic lateral sclerosis. *Hum. Mol. Genet.* http://dx.doi.org/10.1093/hmg/dds116.
130. Ticozzi, N. *et al.* Mutational analysis reveals the FUS homolog *TAF15* as a candidate gene for familial amyotrophic lateral sclerosis. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **156**, 285–290 (2011).
131. Dormann, D. *et al.* ALS-associated fused in sarcoma (*FUS*) mutations disrupt Transportin-mediated nuclear import. *EMBO J.* **29**, 2841–2857 (2010).
132. Ito, D., Seki, M., Tsunoda, Y., Uchiyama, H. & Suzuki, N. Nuclear transport impairment of amyotrophic lateral sclerosis-linked mutations in FUS/TLS. *Ann. Neurol.* **69**, 152–162 (2010).
133. Belyanskaya, L. L., Delattre, O. & Gehring, H. Expression and subcellular localization of Ewing sarcoma (EWS) protein is affected by the methylation process. *Exp. Cell Res.* **288**, 374–381 (2003).
134. Jobert, L., Argentini, M. & Tora, L. PRMT1 mediated methylation of TAF15 is required for its positive gene regulatory function. *Exp. Cell Res.* **315**, 1273–1286 (2009).
135. Rappsilber, J., Friesen, W. J., Paushkin, S., Dreyfuss, G. & Mann, M. Detection of arginine dimethylated peptides by parallel precursor ion scanning mass spectrometry in positive ion mode. *Anal. Chem.* **75**, 3107–3114 (2003).
136. Fronz, K. *et al.* Arginine methylation of the nuclear poly(A) binding protein weakens the interaction with its nuclear import receptor, transportin. *J. Biol. Chem.* **286**, 32986–32994 (2011).
137. Deloulme, J. C., Prichard, L., Delattre, O. & Storm, D. R. The prooncoprotein EWS binds calmodulin and is phosphorylated by protein

kinase C through an IQ domain. *J. Biol. Chem.* **272**, 27369–27377 (1997).
138. Perrotti, D. *et al.* TLS/FUS, a pro-oncogene involved in multiple chromosomal translocations, is a novel regulator of BCR/ABL-mediated leukemogenesis. *EMBO J.* **17**, 4442–4455 (1998).
139. Leemann-Zakaryan, R. P., Pahlich, S., Grossenbacher, D. & Gehring, H. Tyrosine phosphorylation in the C-terminal nuclear localization and retention signal (C-NLS) of the EWS protein. *Sarcoma* **2011**, 218483 (2011).
140. Page, T. *et al.* FUS immunogold labeling TEM analysis of the neuronal cytoplasmic inclusions of neuronal intermediate filament inclusion disease: a frontotemporal lobar degeneration with FUS proteinopathy. *J. Mol. Neurosci.* **45**, 409–421 (2011).
141. Lanson, N. A. Jr & Pandey, U. B. FUS-related proteinopathies: lessons from animal models. *Brain Res.* http://dx.doi.org/10.1016/j.brainres.2012.01.039.
142. Josephs, K. A. *et al.* Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol.* **122**, 137–153 (2011).
143. Rohrer, J. D. & Warren, J. D. Phenotypic signatures of genetic frontotemporal dementia. *Curr. Opin. Neurol.* **24**, 542–549 (2011).
144. Hu, W. T., Trojanowski, J. Q. & Shaw, L. M. Biomarkers in frontotemporal lobar degenerations–progress and challenges. *Prog. Neurobiol.* **95**, 636–648 (2011).
145. Noto, Y. *et al.* Elevated CSF TDP-43 levels in amyotrophic lateral sclerosis: specificity, sensitivity, and a possible prognostic value. *Amyotroph. Lateral Scler.* **12**, 140–143 (2011).
146. Time is ripe for clinical trials in frontotemporal degeneration. *Alzheimer Research Forum* [online], http://www.alzforum.org/new/pdf/FTLDSeries.pdf (2011).
147. Pick, A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie [German]. *Prager medicinische Wochenschrift* **17**, 165–167 (1892).
148. Alzheimer, A. Über eigenartige Krankheitsfäelle des späeteren Alters [German]. *Z. Gesamte Neurol. Psychiatrie* **4**, 356–385 (1911).
149. Rebeiz, J. J., Kolodny, E. H. & Richardson, E. P. Jr. Corticodentatonigral degeneration with neuronal achromasia. *Arch. Neurol.* **18**, 20–33 (1968).
150. Steele, J. C., Richardson, J. C. & Olszewski, J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch. Neurol.* **10**, 333–359 (1964).
151. Constantinidis, J., Richard, J. & Tissot, R. Pick's disease. Histological and clinical correlations. *Eur. Neurol.* **11**, 208–217 (1974).
152. Lee, V. M., Goedert, M. & Trojanowski, J. Q. Neurodegenerative tauopathies. *Annu. Rev. Neurosci.* **24**, 1121–1159 (2001).
153. Knopman, D. S., Mastri, A. R., Frey, W. H. 2nd, Sung, J. H. & Rustan, T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. *Neurology* **40**, 251–256 (1990).
154. Jackson, M., Lennox, G. & Lowe, J. Motor neurone disease-inclusion dementia. *Neurodegeneration* **5**, 339–350 (1996).
155. Mackenzie, I. R., Foti, D., Woulfe, J. & Hurwitz, T. A. Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain* **131**, 1282–1293 (2008).
156. Roeber, S., Mackenzie, I. R., Kretzschmar, H. A. & Neumann, M. TDP-43-negative FTLD-U is a significant new clinico–pathological subtype of FTLD. *Acta Neuropathol.* **116**, 147–157 (2008).
157. Laaksovirta, H. *et al.* Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. *Lancet Neurol.* **9**, 978–985 (2010).
158. Shatunov, A. *et al.* Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. *Lancet Neurol.* **9**, 986–994 (2010).
159. van Es, M. A. *et al.* Genome-wide association study identifies 19p13.3 (*UNC13A*) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. *Nat. Genet.* **41**, 1083–1087 (2009).

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